J. Perinat. Med.
17 (1989) 453

Beta-2-microglobulin in the assessment of renal function in full term newborns following perinatal asphyxia

Fernando Fernandez[2], Vicente Barrio[1], Juana Guzman[2], Maria Dolores Huertas[2], Mercedes Zapatero[2], Maria Dolores de Miguel[2], and Jesus Mallol[3]

[1]Service of Nephrology, [2]Unit of Neonatology, Department of Pediatrics, and [3]Service of Nuclear Medicine, "Reina Sofia" Hospital, Córdoba, Spain

1 Introduction

Perinatal asphyxia has been recognized as a cause of acute renal failure (ARF) in the newborn [1, 8, 19]. The initial response to intrauterine hypoxia is a redistribution of cardiac output with a decrease in renal perfusion among other organs, in order to preserve perfusion to vital organs including brain, heart, and adrenal glands [4, 6]. Renal proximal tubule is particularly susceptible to hypoxia [20], as reflected by a marked decrease in reabsorption capacity following this insult. Beta-2 microglobulin (β_2-m) is a low molecular weight protein freely filtered through the glomerular capillary wall and almost completely reabsorbed by proximal tubular cells. Therefore, urinary excretion of β_2-m is very small [18, 21]. Tubular damage secondary to hypoxia [7, 22], ischemia [13], and nephrotoxic agents [2, 11] results in increased urinary levels of β_2-m.

The aim of the present study was to evaluate the clinical usefulness of β_2-m determination in serum and urine in the diagnosis of renal dysfunction in full term neonates following asphyxia, and to compare these tests with traditional indices of renal function such as plasma creatinine (Cr), endogenous creatinine clearance (Ccr), and fractional sodium excretion.

2 Methods

From December 1986 through March 1988, forty full term newborns were studied. The group of asphyxiated infants comprised twenty newborns with a mean birth weight of 3180 ± 325 g, all of which met at least three of the following criteria:

1. Abnormal fetal heart rate monitoring
2. Apgar score under 4 at one minute, and under 6 at five minutes of life
3. Requirement for more than one minute of positive pressure ventilation before spontaneous sustained respiration occurred
4. Metabolic acidosis with pH < 7.2 within twenty minutes of birth.

The control group included twenty full term infants with a mean birth weight of 3271 ± 295 g who were delivered normally after an uncomplicated pregnancy. None of them presented clinical nor biochemical signs of asphyxia.

Curriculum vitae

FERNANDO FERNANDEZ, *M.D., was graduated from Cantabria University in 1979 and qualified as a specialist in Pediatrics at Children's Hospital "La Paz" Madrid, Spain in 1984. He had a fellowship in Neonatology at the same Hospital in 1984. Since 1986 he has been on the staff of Department of Pediatrics, Children's Hospital "Reina Sofia", Córdoba, Spain. His main research interest is in the field of perinatal asphyxia.*

None of the infants showed major congenital abnormalities, respiratory distress syndrome, cardiac dysfunction, hyperbilirubinemia, renal disease nor received nephrotoxic drugs. All asphyxiated infants were given 60 ml/kg of iv fluid (10% dextrose in water) on the first day of life. Fluid and electrolyte intake was subsequently adjusted according to patient's clinical status. Infants in the control group received formula during the first four to six hours after birth and were thereafter fed ad libitum every three hours.

Renal function was evaluated in both groups on the first and third day of life by means of serum and urinary levels of creatinine, sodium, and β_2-m. Timed 8 hours urine samples were collected using a urine bag placed over the infant's external genitalia. Manual suprapubic pressure was applied at the end of the collection interval to ensure completeness. When urinary pH was less than 6.0, alkalinazation was obtained with sodium hydroxide to prevent β_2-m inactivation. At the midpoint of urine collection, 3 ml of blood were drawn from an umbilical catheter or peripheral vein and immediately centrifuged. Serum and urine samples were stored at $-20\,^{\circ}C$ until analyzed. β_2-m was measured by radioimmunosorbent assay (Phadebas, β2 microtest, Pharmacia Diagnostics, Uppsala, Sweden).

Creatinine clearance, fractional excretion of sodium (FeNa), and fractional excretion of β_2-m ($Fe\beta_2$-m) were calculated as follows:

$$Ccr\ (ml/min\ 1.73\ m^2) = (V\ Ucr/Pcr)\ (1.73/BSA)$$

$$CNa\ (ml/min\ 1.73\ m^2) = (V\ UNa/PNa)\ (1.73/BSA)$$

$$FeNa\ (\%) = CNa/Ccr$$

$$C\beta_2\text{-}m\ (ml/min\ 1.73\ m^2) = (V\ U\beta_2\text{-}m/P\beta_2\text{-}m)\ (1.73/BSA)$$

$$Fe\beta_2\text{-}m\ (\%) = C\beta_2\text{-}m/Ccr$$

where BSA = Body Surface Area, C = Clearance, Na = Sodium (mEq/l), Cr = creatinine (mg/dl), V = Urine flow (ml/min), P = Plasma, U = Urine.

All results are given as the mean ± one standard deviation. Statistical analysis was performed with Statistical Analysis System (SAS) software [17], and included Student's t test for unpaired data, and repeated measures analysis of variance. Multiple comparisons were adjusted according to Scheffe's multiple F tests on all main-effect means. Correlation coefficients were determined; P values < 0.05 were considered significant. Sensitivity, and specificity of urinary β_2-m/Cr ratio, $Fe\beta_2$-m, and FeNa as indices of proximal tubular injury following asphyxia were evaluated.

3 Results

In the group of asphyxiated infants, 11 out of 20 presented oliguria defined by a urinary flow rate of less than 0.8 ml/kg per hour and 5 oliguric acute renal failure defined by a urinary flow rate of less than 1.0 ml/kg per hour which failed to respond to volume repletion along with serum creatinine greater than 1.5 mg/dl. Ten asphyxiated infants with oliguria presented Apgar scores under 4 at 5 minutes of life and pH < 7.10.

A summary of global results on the first and third day of life for both groups of patients is displayed on table I. Significant differences between controls and asphyxiated full term infants were found, on both day 1 and 3, for serum creatinine ($p < 0.01$), endogenous creatinine clearance ($p < 0.01$), urinary β_2-m/creatinine ratio ($p < 0.01$), fractional Na excretion ($p < 0.01$), and fractional excretion of β_2-m ($p < 0.01$). On the other hand, no differences were observed in serum β_2-m.

In asphyxiated neonates stratified by the presence or absence of oliguria or acute renal failure as defined above (table II), infants with oliguria presented significantly higher values of serum creatinine ($p < 0.05$) and $Fe\beta_2$-m ($p < 0.05$) on the first day of life. Urinary β_2-m/creatinine ratio was only significantly increased in infants with oliguria. On day 3, serum creatinine levels were only significantly elevated in asphyxiated infants with acute renal failure. No significant differences in creatinine clearance, FeNa, urinary β_2-m/creatinine, nor in $Fe\beta_2$-m were observed.

In asphyxiated infants on the first day of life, urinary β_2-m/creatinine ratio was significantly correlated with serum β_2-m ($r = 0.48$, $p < 0.05$), FeNa ($r = 0.59$, $p < 0.01$), and with $Fe\beta_2$-m ($r = 0.70$, $p < 0.01$), but not with serum creatinine. $Fe\beta_2$-m was significantly correlated with FeNa ($r = 0.66$, $p < 0.66$, $p < 0.01$), but neither with serum β_2-m, serum creatinine, nor with creatinine clearance. FeNa was not correlated with serum creatinine and neither with creatinine clearance. On day 3, urinary β_2-m/creatinine ratio correlated with FeNa ($r = 0.52$, $p < 0.05$), and with $Fe\beta_2$-m ($r = 0.53$, $p < 0.05$). Addition-

Table I. Summary of traditional renal function tests and determinations of β_2-m in serum and urine

	Serum Cr (mg/dl)	Cr Clearance (ml/min 1.73 m^2)	FeNa (%)	Serum β_2-m (μg/ml)	Urinary β_2-m/Cr (μg/mg)	Feβ_2-m (%)
Controls:						
First day	0.8 ± 0.1	31.7 ± 5.2	0.4 ± 0.2	3.4 ± 0.5	22.4 ± 11.7	4.9 ± 3.0
Third day	0.6 ± 0.1	35.2 ± 7.9	0.3 ± 0.1	3.4 ± 0.5	21.1 ± 9.6	3.8 ± 1.9
Asphyctic:						
First day	1.1 ± 0.2*	21.3 ± 4.9*	1.2 ± 0.5*	4.1 ± 1.6	62.2 ± 31.6*	16.5 ± 11.5*
Third day	0.9 ± 0.3*	27.4 ± 7.8*	1.0 ± 0.5*	3.7 ± 1.4	52.5 ± 18.0*	13.8 ± 9.4*

Between groups comparisons on the same day *$p < 0.01$.

Table II. Summary of tests stratified by the presence of oliguria and of acute renal failure

	Serum Cr (mg/dl)	Cr Clearance (ml/min 1.73 m^2)	FeNa (%)	Urinary β_2-m/Cr (μg/mg)	Feβ_2-m (%)
Oliguria: (11)					
First day	1.3 ± 0.3	20.2 ± 5.6	1.5 ± 0.7	78.3 ± 42.2	22.7 ± 13.5
Third day	0.9 ± 0.4	24.0 ± 7.7	1.0 ± 0.6	57.0 ± 30.4	16.0 ± 11.3
Normal diuresis:					
First day	1.0 ± 0.1*	22.1 ± 4.0	1.1 ± 0.4	49.0 ± 26.3*	11.6 ± 5.7*
Third day	0.9 ± 0.3	24.8 ± 7.7	0.9 ± 0.4	48.8 ± 26.9	12.5 ± 7.1
ARF: (5)					
First day	1.5 ± 0.1	16.8 ± 2.7	1.6 ± 0.6	65.2 ± 35.0	26.4 ± 11.4
Third day	1.6 ± 0.4	22.0 ± 6.2	1.0 ± 0.4	50.6 ± 20.8	14.6 ± 4.3
Normal function:					
First day	1.0 ± 0.9*	22.8 ± 4.3*	1.2 ± 0.6	61.2 ± 44.7	13.3 ± 7.5*
Third day	0.9 ± 0.3*	25.2 ± 7.9	1.0 ± 0.5	53.1 ± 30.7	13.6 ± 10.5

Numbers in parentheses represent n. Within groups comparisons on the same day *$p < 0.05$.

ally, Feβ_2-m was significantly correlated with FeNa ($r = 0.78$, $p < 0.01$).

Values situated two standard deviations above the mean of the control group were considered as the upper limit of normal. According to this, on the first day of life 14 out of 20 asphyxiated neonates in contrast to only 1 neonate in the control group had elevated urinary β_2-m/creatinine ratio. Similarly, 15 out of 20 asphyxiated neonates and 1 in the control group had elevated levels of Feβ_2-m. Finally, 13 out of 20 asphyxiated neonates and 3 out of 20 in the control group presented elevated levels of FeNa. Sensitivity of urinary β_2-m/creatinine ratio, Feβ_2-m, and FeNa were 0.70, 0.75, and 0.65, and specificity 0.95, 0.95, and 0.85 respectively.

4 Discussion

Results of the present study demonstrate that perinatal hypoxia causes impairment of tubular function as evidenced by an increase in urinary β_2-m/creatinine ratio, fractional excretion of β_2-m, and fractional excretion of Na. The degree

of tubular dysfunction seems to be related to the severity of the ischemic insult since those neonates with more severe asphyxia, reflected by lower blood pH and Apgar scores, developed oliguria and/or acute renal failure, and had the highest levels of urinary β_2-m/creatinine ratio and Feβ_2-m on the first day of life.

Values of serum β_2-m of the present study in the control group are consistent with previous reports [10, 3, 23]. There were no differences in serum β_2-m levels between the control group and those of asphyxiated infants. Additionally, serum β_2-m was neither correlated with serum creatinine nor with creatinine clearance. This precludes the use of serum β_2-m as an index of glomerular filtration rate in neonates, in contrast to adults where several studies have pointed out to its usefulness [5, 14].

Since it has been suggested that urinary β_2-m may be dependent on urine flow rate [10], although the point is controversial, urinary β_2-m was factored by urinary creatinine. Values of urinary β_2-m/creatinine ratio and Feβ_2-m in the control group are similar to those reported in the literature [10, 3]. Urinary β_2-m/creatinine ratio and Feβ_2-m in the present study have shown significant increases both on the first and third day after asphyxia with respect to the control group.

When comparison was restricted to the neonates stratified by the presence or absence of oliguria or acute renal failure, only urinary β_2-m/creatinine ratio and Feβ_2-m during the first day were significantly increased. Two previous reports indicate increased levels of urinary β_2-m secondary to proximal tubular dysfunction following perinatal hypoxia. COLE et al. [7], in a study including 65 full term newborns, found that infants with meconium stained amniotic fluid, mainly those with low Apgar score, presented elevated urinary β_2-m levels. Recently, TACK et al. [22] described elevated urinary β_2-m levels in preterm and term asphyctic newborns. Urinary β_2-m/creatinine ratios in the present study display lower values, probably due to the inclusion in their study of preterm newborns, many of them less than 35 weeks which is the time when glomerular tubular balance is established [3]. Since serum β_2-m and urinary β_2-m/creatinine ratio were not correlated and did not differ significantly between control and asphyctic groups, we may suggest that serum β_2-m levels did not contribute to urinary β_2-m levels. Likewise, since no tubular maximum (Tm) for human β_2-m reabsorption has been found [12], the filtered load of β_2-m has little, if any, effect on urinary β_2-m levels.

FeNa has commonly been used to estimate renal tubular function in neonates [15, 16, 9]. Usually, a FeNa greater than 2.5 to 3% is present in most neonates with oliguric acute renal failure [16]. ELLIS and ARNOLD [9] found that a FeNa above 2.5% was present in all neonates with oliguric acute renal failure, but unfortunately similar figures were found in infants with prerenal oliguria. In the present study, although we observed elevated FeNa values in the group of asphyxiated neonates, FeNa was not able to discriminate between the presence or absence of oliguria or acute renal failure. On the first day of life, only 1 out of 5 of those infants who developed acute renal failure presented FeNa levels above 2.5%. Therefore, FeNa seems to be less sensitive and specific than urinary β_2-m/creatinine ratio or Feβ_2-m to identify tubular proximal dysfunction following perinatal asphyxia.

In summary, in the present study, urinary β_2-m/creatinine ratio and fractional excretion of β_2-m appear to be sensitive and specific tests for the early detection of renal proximal tubular dysfunction following perinatal asphyxia, providing better information than that obtained through traditional tests of renal function.

Abstract

In order to evaluate the clinical usefulness of serum and urinary β_2 microglobulin (β_2-m) determination as a marker of renal damage following perinatal asphyxia, twenty asphyxiated and twenty healthy full term newborns were studied. Renal function was monitored on the first and third day after birth by traditional tests such as creatinine (Cr), endogenous creatinine clearance (Ccr), and fractional Na excretion (FeNa), as well as by serum and urinary β_2 microglobulin. The value of different tests for the diagnosis of oliguria and of acute renal failure was determined. Eleven asphyxiated neonates developed oliguria and five ARF in contrast to none of the controls. Both traditional tests of renal function, and determinations of β_2-m with the exception of serum β_2-m, were significantly different ($p < 0.01$) between controls and asphyxiated

neonates. When stratified analysis was performed, only serum cr, urinary β_2-m/cr ratio, and Feβ_2-m were able to discriminate oliguria from preserved diuresis on the first day of life. For ARF, only Ccr and Feβ_2-m were different, again on the first day of life. Urinary β_2-m/creatinine ratio and Feβ_2-m appear to be more sensitive and specific for the early detection of proximal tubular renal dysfunction following perinatal asphyxia than usual tests of renal function.

Keywords: β_2 microglobulin, perinatal asphyxia, renal function tests, sensitivity, specificity.

Zusammenfassung

β_2-Mikroglobulin als Parameter der Nierenfunktion bei Reifgeborenen nach perinataler Asphyxie

Um die Brauchbarkeit einer β_2-Mikroglobulin-Bestimmung (β_2-m) im Serum und Urin als Marker einer renalen Schädigung nach perinataler Asphyxie zu überprüfen, untersuchten wir 20 reife, asphyktische Neugeborene, auf die mindestens 3 der folgenden Kriterien zutrafen: 1. Pathologisches CTG. 2. Apgar-Score unter 4 eine Minute p. p. und unter 6 fünf Minuten p. p. 3. Notwendigkeit einer Beatmung mit positiven Drucken über mehr als eine Minute. 4. Metabolische Azidose mit einem pH < 7,2 in den ersten 20 Minuten. Zwanzig gesunde Neugeborene dienten als Kontrollgruppe. Am ersten und dritten Lebenstag wurde die Nierenfunktion durch konventionelle Methoden wie Creatininbestimmung (Cr), endogene Creatinin-Clearance (Ccr) und fraktionierte Natrium-Ausscheidung (FeNa) sowie auch durch radioimmunologische Messung des β_2-Mikroglobulins im Urin (Feβ_2-m) und Serum bestimmt. Bei der Analyse der Daten erfolgte auch eine Zuordnung zu einer aufgetretenen Oligurie (Harnfluß geringer als 0,8 ml/kg/h) bzw. zu einem akuten Nierenversagen (Harnfluß geringer als 1,0 ml/kg/h, bei Volumenauffüllung keine Reaktion, Creatinin im Serum höher als 1,5 mg/dl).

Elf asphyktische Neugeborene entwickelten eine Oligurie und fünf ein akutes Nierenversagen. Beide Komplikationen traten in der Kontrollgruppe nicht auf. Sowohl die konventionellen Tests wie auch das β_2-m im Urin, nicht aber das β_2-m im Serum lieferten signifikant unterschiedliche Werte ($p < 0,01$) zwischen Asphyxie- und Kontrollgruppe (Tab. I). Bei Klassifizierung (Tab. II) zeigte sich, daß hinsichtlich der Oligurie nur das Serumcreatinin, die β_2-m/Cr-Ratio und das Feβ_-m in der Lage waren, am ersten Lebenstag zwischen einer Oligurie und einer verzögerten Diurese zu unterscheiden. Bezogen auf ein akutes Nierenversagen waren am ersten Lebenstag lediglich Ccr und Feβ_2-m unterschiedlich. Am dritten Lebenstag fanden sich in allen Gruppen mit Ausnahme des Creatinin, nach dessen Höhe ein akutes Nierenversagen definiert wurde, keine Unterschiede. Die Sensitivität der β_2-m/Cr-Ratio im Urin, des Feβ_2-m und der FeNa betrug 0,70, 0,75 und 0,65, die Spezifität lag bald bei 0,95, 0,95 und 0,85.

Im Gegensatz zu Erwachsenen kann bei Neugeborenen das Serum-β_2-m nicht als Parameter der glomerulären Filtrationsrate angesehen werden. Der Schaden im proximalen Tubulus nach Asphyxiw führt zu einer verminderten Reabsorption von β_2-m und daraus folgend zu einer erhöhten β_2-m/Cr-Ratio im Urin wie auch eines vermehrten Feβ_2-m bei Oligurie. Nach der FeNa ist weder eine Zuordnung zu der Gruppe mit Oligurie noch zur Gruppe mit eingeschränkter Nierenfunktion möglich. Wir glauben daher, daß die β_2-m/Cr-Ratio im Urin und die Feβ_2-m sensitive und spezifische Tests zur frühen Erkennung einer Störung des proximalen Tubulus nach perinataler Asphyxie darstellen.

Schlüsselwörter: β_2-Mikroglobulin, Nierenfunktiontests, perinatale Asphyxie, Sensitivität, Spezifizität.

Résumé

La β_2 microglobuline dans l'appreciation de la fonction renale des nouveaux-nes a terme apres asphyxie perinatale

On a étudié vingt nouveaux-nés à terme ayant subi une asphyxie avec au moins trois des critères suivants: 1. surveillance du rythme cardiaque anormale, 2. score d'Apgar inférieur à 4 à une minute, et inférieur à 6 à 5 minutes de vie, 3. nécessité d'une ventilation à pression positive supérieure à une minute, 4. acidose métabolique avec pH < 7,2 au cours des 20 minutes après la naissance, ainsi que vingt nouveaux-nés à terme bien portants afin d'évaluer l'utilité clinique du dosage sérique et urinaire de la β_2 microglobuline (β_2-m) comme marqueur de lésions rénales secondaires à une asphyxie périnatale. On a surveillé la fonction rénale au premier et au troisième jour après la naissance au moyen des tests traditionnels tels que la créatinine (Cr), la clearance de la créatinine endogène (Ccr) et l'excrétion fractionnelle du sodium (FeNa), ainsi que au moyen du dosage radio-immunologique sérique et urinaire de la β_2 microglobuline. On a analysé les données pour le groupe dans son ensemble et après réalisation de sous groupes en fonction de la présence d'une oligurie définie par un débit urinaire inférieur à 0,8 ml/Kg/heure

et d'une insuffisance rénale aigüe (IRA) définie par un débit urinaire inférieur à 1,0 ml/Kg/heure, ne répondant pas à un remplissage avec une créatinine sérique supérieure à 1,5 mg/dl.
Onze nouveaux-nés asphyxiés ont présenté une oligurie et cinq une IRA, contre aucun des témoins. Tous les tests traditionnels de la fonction rénale ainsi que les dosages de la β_2-m, à l'exception de la β_2-m sérique, étaient significativement différents ($p < 0,01$) entre les nouveaux-nés témoins et asphyxiés (tableau I). Avec l'analyse des sous-groupes (tableau II) seuls la Cr sérique, le ratio β_2-m urinaire/Cr et Feβ_2m permettent de discriminer l'oligurie de la diurèse conservée au cours du premier jour de vie. En ce qui concerne l'IRA, seuls la Ccr et la Feβ_2-m étaient différents, également au cours du premier jour de vie. On n'a pas observé de différences au troisième jour quel que soit le groupe, à l'exception de la Cr qui est utilisée pour définir l'IRA.
Les sensibilités du ratio β_2-m urinaire/créatinine, de la Feβ_2-m et de la FeNa sont de 0,70, 0,75 et de 0,65 et les spécificités respectivement de 0,95, 0,95 et de 0,85. En contraste avec la situation des adultes, la β_2-m sérique ne peut être utilisée chez les nouveaux-nés comme index du taux de filtration glomérulaire. Les lésions tubulaires proximales rénales secondaires à une asphyxie périnatale semblent rendre compte de la capacité réduite de réabsorption de la β_2-m et par là, de l'augmentation du ratio β_2-m urinaire/Cr et de la Fe β_2-m trouvée en présence d'une oligurie. Le FeNA n'est pas utile pour placer le nouveau-né ni dans le groupe oligurique ni dans le groupe avec fonction rénale réduite. Ainsi, le ratio β_2-m urinaire/créatinine et la Feβ_2-m apparaissent être des tests sensibles et spécifiques pour le dépistage précoce de la dysfonction tubulaire proximale rénale secondaire à l'asphyxie périnatale.

Mots-clés: Asphyxie périnatale, β_2 microglobuline, sensibilité, spécificité, tests de la fonction rénale.

Acknowledgement: This study was supported by a grant from Heinz Koch Foundation, 1988.

References

[1] ANAND SK: Acute renal failure in the neonate. Ped Clin North Am 29 (1982) 791
[2] ASSADI FK, E CHOW-TUNG: Renal handling of beta-2-microglobulin in neonates treated with gentamicin. Nephron 49 (1988) 114
[3] ASSADI FK, EG JOHN, P JUSTICE, L FORNELL: β_2 microglobulin clearance in neonates: index of tubular maturation. Kidney Int 28 (1985) 153
[4] BERHMAN RE, MH LEES, EN PETERSON, CW DE LANNOY, AE SEEDS: Distribution of the circulation in the normal and asphyxiated fetal primate. Am J Obstet Gynecol 108 (1970) 956
[5] CEJKA J, C FLOSSIE, K KITHIER: Serum β_2-microglobulin levels in normal children and sex-linked agammaglobulinemia patients. Clin Chim Acta 47 (1973) 59
[6] COHN HE, EJ SACKS, MA HEYMANN, AM RUDOLPH: Cardiovascular responses to hypoxemia and ischemia in fetal lambs. Am J Obstet Gynecol 120 (1974) 817
[7] COLE JW, RJ PORTMAN, Y LIN, JM PERLMAN, AM ROBSON: Urinary β_2-microglobulin in full terms newborns: evidence for proximal tubular dysfunction in infants with meconium stained amniotic fluid. Pediatrics 76 (1985) 958
[8] DAUBER IM, AN KRAUSS, PS SYMCHYCH, PAM AULD: Renal failure following perinatal anoxia. J Pediatr 88 (1976) 851
[9] ELLIS EN, WC ARNOLD: Use of urinary indexes in renal failure in the newborn. Am J Dis Child 136 (1982) 615
[10] ENGLE WD, BS ARANT: Renal handling of beta-2-microglobulin in the human neonate. Kidney Int 24 (1983) 358
[11] GOUYON JB, Y AUJARD, A ABISROR, N LAUDIGNON, P D'ATHIS, E JACQZ, D BIOU, JF DEMELIER, H MATHIEU: Urinary excretion of N-Acetyl-Glucosaminidase and beta-2-microglobulin as early markers of gentamicin nephrotoxicity in neonates. Rev Pharmacol Ther 10 (1987) 145
[12] HALL PW, M CHUNG-PARK, CV VACCA, M LONDON, AQ CROWLEY: The renal handling of beta 2-microglobulin in the dog. Kidney Int 22 (1982) 156
[13] HALL PW, ES RICANATI: Renal handling of β_2 microglobulin in renal disorders: with special reference to hepatorenal syndrome. Nephron 27 (1981) 62
[14] LEROY D, F MAURIAT, M DECHAUX, N CHOPIN, M BROYERS, C SACHS: La β_2 microblobuline: index de la filtration glomerulaire chez l'enfant. Arch Fr Pediatr 41 (1984) 43
[15] MATHEW OP, AS JONAS, E JAMES, H BLAND, T GROSHONG: Neonatal renal failure: usefulness of diagnostic indices. Pediatrics 65 (1980) 57
[16] NORMAN ME, FK ASSADI: A prospective study of acute renal failure in the newborn infant. Pediatrics 63 (1979) 475
[17] SAS User's Guide. 5th Ed. Cary, North Carolina: SAS institute, Inc. 1985
[18] SCHARDIJN GHC, LW STATIUS VAN EPS: β_2 microglobulin: its significance in the evaluation of renal function. Kidney Int 32 (1987) 635

[19] STAPELTON FB, DP JONES, RS GREEN: Acute renal failure in neonates: incidence, etiology, and outcome. Pediatr Nephrol 1 (1987) 314

[20] STARK H, R GEIGER: Renal tubular dysfunction following vascular accidents of the kidneys in the newborn period. J Pediatr 83 (1973) 933

[21] STATIUS VAN EPS LW, GHC SCHARDIJN: β_2 microglobulin and the renal tubule. In: LUBEC G (ed): Non-invasive diagnosis of kidney disease. Karger, Basel 1983, 103

[22] TACK ED, JM PERLMAN, AM ROBSON: Renal injury in sick newborn infants: a prospective evaluation using urinary β_2-microglobulin concentrations. Pediatrics 81 (1988) 432

[23] TAKIEDDINE F, M TABBARA, P HALL, RJ SOKOL, KC KING: Fetal renal maturation. Studies on urinary beta 2 microglobulin in the neonate. Acta Obstet Gynecol Scand 62 (1983) 311

Received August 24, 1989. Accepted October 16, 1989.

Dr. Vicente Barrio
Departamento de Nefrologia
Hospital "Reina Sofia"
Avda. Menéndez Pidal s/n
14004 Córdoba, Spain